# The International Liver Congress 2018

Walter Alexander

The European Association for the Study of the Liver International Liver Congress 2018, held in Paris from April 11 to 15, featured key sessions on a range of pharmacological aspects of treatment for liver disease. Included in this report are sessions on drug therapies and strategies for hepatitis C, primary biliary cholangitis, nonalcoholic steatohepatitis, homozygous familial hypercholesterolemia, and advanced hepatocellular carcinoma.

## Early Corticosteroid Treatment in Patients With Indeterminate Acute Severe Hepatitis

- Elisabeth Mohr, MD, University of Leipzig, Leipzig, Germany

Early corticosteroid therapy is warranted in patients with acute severe hepatitis when autoimmune hepatitis (AS-AIH) or drug-induced liver injury (DILI) is suspected, Dr. Mohr said in a poster presentation. In routine clinical practice, early corticosteroids are not often prescribed.

Because it is challenging to discriminate between AS-AIH and DILI, determining whether early corticosteroid therapy would prevent progression to acute liver disease and the need for transplantation would be valuable in either case. Accordingly, Dr. Mohr and colleagues conducted a retrospective analysis of 1,039 patients presenting with acute severe hepatitis (defined as alanine aminotransferase [ALT] greater than five times the upper limit of normal) in two German liver disease centers. They learned that of 179 patients treated with early corticosteroid therapy, 67 were diagnosed with AS-AIH, 52 with DILI, and 56 with other diseases (steatohepatitis, alcoholic hepatitis, etc.). Testing showed that only 34% of patients with AS-AIH had positive scores, with 34% and 32% registering as indeterminate or negative, respectively.

It was of note, Dr. Mohr said, that patients with DILI had significantly higher Mayo End-Stage Liver Disease (MELD) scores than patients with autoimmune hepatitis (mean MELD score of 21 [range, 6–40] versus mean MELD score of 15 [range, 6–26], respectively; $P < 0.01$). In parallel, initial ALT values were higher for DILI patients (mean, 1,846 units/L versus mean, 1,208 units/L; $P = 0.01$). ALT decreased significantly faster among DILI patients receiving corticosteroids ($P < 0.01$), who then required a shorter course of therapy (mean, 87 days versus mean, 366 days; $P < 0.0001$). In addition, AS-AIH patients often had ALT flares with steroid tapering, requiring intensified immunosuppressive regimens.

For AS-AIH and DILI patients respectively, one-year patient survival was 97% and 95%. Infection rates were low (7% mild; 6% severe) in the entire cohort. Liver transplantation was required in seven patients (6%) in the DILI cohort who had higher MELD scores, with one-year transplant survival of 85%.

"Early corticosteroid therapy is warranted in patients with AS-AIH suspected to be of autoimmune or drug-induced etiology because it provides good response and survival rates and helps avoid liver transplantation," Dr. Mohr concluded.

## First Real-World Data on Safety and Effectiveness Of Glecaprevir/Pibrentasvir for the Treatment of Patients With Chronic Hepatitis C Virus Infection: Data From the German Hepatitis C Registry

- Thomas Berg, MD, University Hospital Leipzig, Leipzig, Germany

The German Hepatitis C Registry, the first real-world data analysis of treatment with glecaprevir/pibrentasvir (Mavyret, AbbVie) among patients with chronic hepatitis C virus (HCV) infection, found both effectiveness and safety to be favorable.

The glecaprevir/pibrentasvir co-formulation of two direct-acting antivirals is approved for the treatment of HCV genotype 1–6 infection, Dr. Berg noted in an International Liver Congress press briefing. He pointed out that while the overall cure rate in clinical trials of glecaprevir/pibrentasvir has been about 98%, real-world data on this regimen are limited.

The ongoing German study includes 638 patients (68% male; median age, 47 years) with HCV genotype 1–6 infection from the registry who have received glecaprevir/pibrentasvir according to the local label. Inclusion criteria allowed patients with or without compensated cirrhosis who were treatment naïve or treatment experienced. Most included patients (90%) were treatment naïve without cirrhosis (93%) and had been treated with glecaprevir/pibrentasvir for eight weeks (92%).

Sustained virological response at 12 weeks after treatment (SVR12), in an interim analysis of a modified intention-to-treat population excluding nonvirological failures, was 100% (49 of 49). Four patients prematurely discontinued treatment for reasons other than virological failure. Although two patients discontinued treatment because of adverse events, no serious (grade 3 or higher) elevations in alanine aminotransferase were observed.

"We have found glecaprevir/pibrentasvir to be a very useful addition to our hepatitis C virus treatment armamentarium," commented press briefing moderator Markus Cornberg, MD, of Hannover Medical School in Germany, "as it simplifies treatment decisions for the majority of patients; glecaprevir/pibrentasvir has the potential to expand the treated population and support the goal of HCV elimination." Dr. Cornberg added that "these data are important because they confirm the high cure rates of more than 98% observed in phase 3 trials. Eight weeks of therapy is possible for all treatment-naïve, noncirrhotic patients, regardless of genotype." He also said that data are lacking in some difficult-to-treat genotype 3 patients, a group with declining prevalence, as shown by the German registry.

*The author is a freelance writer living in New York City.*

## Real-Life Effectiveness and Safety of Glecaprevir/Pibrentasvir Among 723 Patients With Chronic HCV: The Navigator-II Study

• Roberta D'Ambrosio, MD, Migliavacca Center for Liver Disease, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

Nearly all of the 723 patients with chronic hepatitis C virus (HCV) infection who were treated with glecaprevir/pibrentasvir (Mavyret, AbbVie) achieved sustained virological responses (SVRs) in interim NAVIGATOR-II study results, Dr. D'Ambrosio said. SVR12 signifies that no HCV RNA is detectable 12 or more weeks after the end of treatment. She noted that the glecaprevir/pibrentasvir co-formulation is a relatively new direct-acting antiviral therapy. Glecaprevir is an NS3/4A protease inhibitor, and pibrentasvir is an NS5A inhibitor.

Prior phase 2 and 3 studies in adults with chronic HCV infection demonstrated high SVR12 rates with a favorable safety profile. Prior to NAVIGATOR-II, no real-world studies in broad patient groups had been reported, Dr. D'Ambrosio said. The Italian NAVIGATOR-II study assessed 723 consecutive patients (49% male; mean age, 58 years) treated according to local glecaprevir/pibrentasvir labeling (12 or 16 weeks of treatment). Fibrosis was determined histologically or noninvasively through liver stiffness measurement. Interim analysis showed 346 of 347 achieving SVR4 (99.7%), and 98% having undetectable HCV at the end of treatment.

Dr. D'Ambrosio reported that only three patients discontinued therapy prematurely. In general, treatment-related adverse events were mild.

She concluded, "Our real-world study involving more than 700 patients with chronic HCV infection confirmed that the effectiveness and safety profile of glecaprevir/pibrentasvir were excellent across a range of different patient types."

## Early Versus Delayed HCV Treatment Provides Increased Health Benefits at Lower Costs: A Pan-Genotypic Cost-Effectiveness Analysis

• Scott Johnson, MD, Medicus Economics LLC, Boston, MA

Earlier treatment with the pan-genotypic co-formulation of glecaprevir/pibrentasvir (Mavyret, AbbVie) is dominant with more quality-adjusted life years (QALYs) gained at lower cost, according to a Scottish cost-effectiveness study of hepatitis C virus infection (HCV) treatment. Dr. Johnson, a health economist, noted that although the co-formulation has demonstrated high efficacy and tolerability compared with previous standards of care, some third-party payers restrict treatment access for patients in the early stages of disease.

Compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), need for liver transplantation, and liver-related death, as well as extrahepatic manifestations (i.e., cardiovascular disease, type-2 diabetes, kidney disease), are among the complications of HCV infection, Dr. Johnson said in an International Liver Congress press briefing.

Dr. Johnson's study evaluated whether treatment at early stages of liver fibrosis would reduce hepatic and extrahepatic manifestation risks and lower the overall downstream medical costs compared with treatment in later disease stages. He developed a model of genotype, fibrosis distribution, and costs from Scottish patient-tracker data and a literature review.

For the analysis, outcomes were stratified according to liver disease fibrosis stages when treatment was initiated (mild, F0–F1; moderate, F2–F3; and advanced/compensated cirrhosis, F4/CC). Liver-related death, Dr. Johnson underscored, can occur at any of these stages. Most patients in the analysis had not received prior treatment (74.6%; 66% male).

When treatment with glecaprevir/pibrentasvir was started at later stages, lifetime risks of liver morbidity and mortality increased. Decompensated cirrhosis risk rose from 4.0% to 8.9% to 11.6% with treatment initiation at stages F0–F1, F2–F3, and F4/CC, respectively. The risk of HCC increased from 1.8% to 4.0% to 35.2%, respectively, and risk of liver-related death increased from 3.8% to 9.1% to 41.1%, respectively. Liver transplant risks rose from 0.4% to 1.0% to 2.6% with treatment started at the same progressive stages. In addition, compensated cirrhosis rates were 12.4% and 23.0% with treatment started at stages F0–F1 and F2–F3, respectively.

While all groups had similar rates of sustained virological response (approximately 99%), lifetime QALYs decreased as treatment was delayed (16.2% for F0–F1; 13.9% for F2–F3, and 10.0% for F4/CC).

Lifetime direct medical costs, including those for extrahepatic manifestations, increased with delayed glecaprevir/pibrentasvir treatment: £32,996 (US $45,473) for stage F0–F1, £35,128 (US $48,411) for stage F2–F3, and £60,963 (US $84,014) for stage F4/CC. Extrahepatic manifestations contributed to an increase of 6.9%, 5.9%, and 3.0% of costs with later treatment for stages F0–F1, F2–F3, and F4/CC, respectively.

The study implies that reimbursement policies restricting HCV infection treatment based on fibrosis stage "ignore the greater QALYs and lower costs related to treating patients early," Dr. Johnson said. Other early glecaprevir/pibrentasvir treatment cost-savings, he added, can be realized because the treatment allows for a shorter, eight-week duration across all genotypes.

## Treatment of HCV Infection With DAAs Is Associated With Lower HCC Recurrence and Improved Survival After Liver Transplant

• Katharina Willuweit, MD, University Hospital, Essen, Germany

Reports that indicate unexpectedly high rates up to 29% for hepatocellular carcinoma (HCC) recurrence following successful antiviral treatment with direct-acting antivirals (DAAs) in some settings have been disconcerting, Dr. Willuweit noted in a poster presentation. The impact of DAA treatment in HCC has not been adequately clarified by prior research, she added. Dr. Willuweit's retrospective study of DAA treatment in patients with hepatitis C virus (HCV) infection after liver transplant, however, found lower HCC recurrence rates and improved survival rates. Furthermore, the high rates of sustained virological response (SVR) produced by DAAs in patients with chronic HCV would suggest reduced HCC rates.

Dr. Willuweit's analysis was based on clinical laboratory and demographic data from 181 patients (73.5% male) who had received liver transplants between 2004 and 2016 at her institution. All included patients had received liver transplants subsequent to HCV cirrhosis with HCC or to HCC not related to HCV. The study aim was to elucidate the influence of DAA application before or early after liver transplantation on HCC recurrence.

Among the patients included in the study, 48.9% had HCV infection, 21.0% had hepatitis B virus infection, and 18.8% had alcoholic steatohepatitis. In addition, nonalcoholic steatohepatitis was present in 9.8% of patients, and primary biliary cholangitis or autoimmune hepatitis was present in 2.8%. Combined ledipasvir/sofosbuvir (Harvoni, Gilead Sciences) plus ribavirin (54.2%) and sofosbuvir/daclatasvir plus ribavirin (25.0%) were the two most common DAA regimens.

Among patients receiving DAA therapy, HCC recurrence was reported significantly less often ($P \leq 0.019$), in 14 of 92 patients with no HCV infection (15.2%), in 16 of 65 patients who had received no DAA therapy (24.6%), and in none of the 24 patients who had received DAA therapy (0%).

"Our findings support the assumption that direct-acting antiviral therapy does not increase the recurrence rate of hepatocellular carcinoma after liver transplantation. Furthermore, we consider direct-acting antiviral therapies to be safe for hepatitis C virus treatment in the setting of liver transplant and history of hepatocellular carcinoma," Dr. Willuweit concluded. Patients receiving DAA therapy showed a significantly lower HCC risk compared with patients who did not receive a DAA-based hepatitis C virus therapy (0% versus 25%), she added.

## Safety and Efficacy of Ravidasvir Plus Sofosbuvir For 12 Weeks in Noncirrhotic and 24 Weeks In Cirrhotic Patients With HCV Genotypes 1, 2, 3, And 6: The STORM-C-1 Phase 2/3 Trial

- Isabelle Andrieux-Meyer, MD, Drugs for Neglected Diseases Initiative, Geneva, Switzerland

Regardless of hepatitis C virus (HCV) genotype, human immunodeficiency virus (HIV) status, and previous interferon experience, the combination of sofosbuvir (Sovaldi, Gilead Sciences) plus ravidasvir (investigational) for 12 weeks in noncirrhotic and for 24 weeks in cirrhotic patients was highly effective in the STORM-C-1 trial, Dr. Andrieux-Meyer said in a poster session.

"While affordable direct-acting antivirals are urgently needed in low- and middle-income countries, access to treatment is hindered by the very high prices of direct-acting antivirals and [a] low level of political commitment to address the hepatitis C virus epidemic," she said. The STORM-C-1 trial is assessing the efficacy, safety, tolerance, and pharmacokinetics of sofosbuvir plus ravidasvir in Malaysia and Thailand, where genotypes 1 and 3 are prevalent.

In the first stage of the trial, once-daily sofosbuvir (400 mg) and ravidasvir (200 mg) were given for 12 weeks in patients with no cirrhosis (n = 219) and for 24 weeks in those with compensated cirrhosis (n = 81). Patients with no current injection-drug use at the eligibility visit who received at least one dose of a study drug were included in the intent-to-treat analysis. The primary endpoint was sustained virological response at 12 weeks post-treatment (SVR12). Forty-four percent had injection-drug use histories, and 30% had HIV co-infection. The median age was 47 years (70% male). Twenty-seven percent of the 300 patients had compensated cirrhosis.

Data analysis showed the overall SVR12 rate to be 97%, significantly higher than the prespecified performance goal of 85% ($P < 0.001$). The overall SVR12 rate in a per-protocol analysis was 98.3% (288 of 293 patients).

No clinically significant drug interactions were observed between ravidasvir and the usual HIV antiretroviral drugs, Dr. Andrieux-Meyer said, and laboratory abnormalities were rare. Abnormalities with alanine aminotransferase occurred in 19 patients; abnormalities with aspartate transaminase occurred in 14 patients. Three patients discontinued treatment prematurely because of adverse events. There were no deaths. The most frequent adverse events were pyrexia (7%), cough (6%), upper respiratory tract infection (5%), and headache (4%). Twenty-nine serious adverse events were reported, with one transient acute renal failure case in an HIV/HCV co-infected patient. In addition, one case of syncope of unknown origin was possibly related to the study drugs. Electrocardiography revealed one case each of prolonged QTc, palpitations, and sinus bradycardia with prolonged QTc at week 12 post-treatment, which were considered possibly related to the study drugs.

The second stage of STORM-C is in preparation and will focus on key subgroups, Dr. Andrieux-Meyer said.

## Long-Term Obeticholic Acid Treatment Associated With Reversal or Stabilization of Fibrosis/Cirrhosis In Patients With Primary Biliary Cholangitis

- Christopher Bowlus, MD, University of California–Davis, Sacramento, California

In patients with primary biliary cholangitis who have had an inadequate response to ursodeoxycholic acid, long-term treatment with obeticholic acid (Ocaliva, Intercept Pharmaceuticals), a potent, selective farnesoid X receptor agonist, may improve disease progression, according to a substudy of the PBC OCA International Study of Efficacy (POISE) trial. The risk of fibrosis progression, liver failure, liver transplant, and death are higher in primary biliary cholangitis patients with inadequate response to ursodeoxycholic acid and in untreated patients, Dr. Bowlus said.

In a phase 2 study in patients with nonalcoholic steatohepatitis, obeticholic acid significantly improved histologic fibrosis compared with placebo treatment. POISE was a 12-month, double-blind, placebo-controlled, phase 3 study of obeticholic acid (5–10 mg) in patients with primary biliary cholangitis, with an open-label extension study of the safety and durability of responses.

In the primary endpoint analysis, patients receiving obeticholic acid had significant improvements in two indicators of liver disease—alkaline phosphatase and bilirubin. Dr. Bowlus's substudy included POISE patients who agreed to undergo paired liver biopsies at or before one year from the start of the double-blind period and three years after it. The extension

period was two years in those randomized to obeticholic acid and three years for those randomized to placebo during the double-blind phase. Fibrosis grades were F0–F5; in order of progression, the grades indicate no fibrosis, periportal fibrosis, bridging fibrosis with rare septa, bridging fibrosis with many septa, incomplete cirrhosis, and cirrhosis. The primary outcome was fibrosis or cirrhosis progression, both of which are directly associated with the worsening of disease, the risk for decompensation, and the need for a liver transplant or with death, Dr. Bowlus noted.

Reviewing the small group of patients with baseline biopsy (n = 27) and paired biopsies sufficient for analysis (n = 13), the mean patient age was 58 years, 92% were women, and the mean duration of primary biliary cholangitis was 9.4 years. A central review of biopsies showed six patients (46%) had a reversal of fibrosis (four by one stage; two by two stages) with worsening by one stage in two patients (15%). In addition, all four patients with baseline cirrhosis showed reversal of fibrosis by at least one stage, and three (75%) improved to fibrosis without cirrhosis. None of the paired biopsy patients had granulomatous destructive cholangitis at baseline or at follow-up. No clear relationship emerged between fibrosis state and other histologic changes.

Dr. Bowlus reported that pruritis (69%), fatigue (45%), arthralgia (38%), and nasopharyngitis, diarrhea, nausea, and extremity pain (all at 31%) were the most common adverse events (occurring in three or more patients). Five serious adverse events in five patients were considered unrelated or unlikely to be related to obeticholic acid.

While acknowledging the small sample size, Dr. Bowlus noted, "We did not see those at lower stages getting worse, so this suggests a real effect." He concluded that most of the patients in the POISE substudy achieved reversal or stabilization of fibrosis/cirrhosis after three years of obeticholic acid treatment.

The phase 4 COBALT study (NCT02308111) is evaluating clinical outcomes with obeticholic acid in patients with primary biliary cholangitis.

## Effects of Rosuvastatin and Pioglitazone Long-Term Therapy on Nonalcoholic Steatohepatitis and Coronary Heart Disease

- Nataliya Virstyuk, MD, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

One year of treatment with a low-dose combination of rosuvastatin and pioglitazone improves both nonalcoholic steatohepatitis (NASH) and post-infarction cardiosclerosis, Dr. Virstyuk said in a poster presentation. Prior research has shown high doses of rosuvastatin are effective in the treatment of both cardiovascular disease and nonalcoholic fatty liver disease.

NASH with fibrosis has been identified as an independent risk factor for cardiovascular disease risk. The aim of Dr. Virstyuk's study was to investigate the effects of both rosuvastatin and pioglitazone at low doses on NASH and coronary heart disease. The investigators randomized 42 NASH patients with stable coronary heart disease and post-infarction cardiosclerosis to rosuvastatin 10 mg/day for one year (Group 1, n = 22) or rosuvastatin 10 mg/day plus pioglitazone 15–30 mg/day for one year (Group 2, n = 20).

After treatment, reductions from baseline in several markers were observed: circulating triglycerides (Group 1, $P = 0.04$; Group 2, $P = 0.006$), low-density lipoprotein-cholesterol (Group 1, $P = 0.02$; Group 2, $P = 0.007$), C-reactive protein (Group 1, $P = 0.03$; Group 2, $P = 0.008$), and N-terminal probrain natriuretic peptide (Group 1, $P = 0.04$; Group 2, $P = 0.009$). Reductions in type IV collagen were also similar (Group 1, $P = 0.06$; Group 2, $P = 0.02$).

Normalization of liver enzymes (i.e., alanine aminotransferase, aspartate transaminase, gamma-glutamyl transpeptidase) was more common in Group 2, as were cardiac structural–functional improvements in left ventricular mass index, left ventricular ejection fraction, and segmental left ventricular contractility.

Decreased, stable, or increased liver fibrosis rates were 27.2%, 40.9%, and 31.9% in Group 1 and 60.0%, 35.0%, and 5.0% in Group 2, respectively. Progression of heart failure from New York Heart Association class II to class III was observed in 18.6% of patients in Group 1 and in 5.0% of patients in Group 2.

"Rosuvastatin and pioglitazone at low doses in combination for one year has metabolic, anti-inflammatory, and antifibrotic effects in nonalcoholic steatohepatitis patients with post-infarction cardiosclerosis and reduces progression of nonalcoholic steatohepatitis and coronary heart disease," Dr. Virstyuk concluded.

## Long-Term Liver Safety of Lomitapide in Patients With HFHC: Three-Year Data from the Lomitapide Observational Worldwide Evaluation Registry

- Dominique Larrey, MD, Centre Hospitalier Universitaire de Montpellier, Hôpital Saint-Eloi, Montpellier, France

While phase 3 research in patients with homozygous familial hypercholesterolemia (HFHC) has shown that lomitapide (Juxtapid, Aegerion Pharmaceuticals) is associated with asymptomatic transaminase elevations and liver-fat accumulation, questions have remained about longer-term effects. Three-year follow-up of the Lomitapide Observational Worldwide Evaluation Registry (LOWER) trial of microsomal triglyceride transfer protein inhibition with lomitapide now confirms that transaminase increases are asymptomatic in this patient population.

Among patients enrolled in LOWER, an international, prospective, multicenter, post-marketing observational cohort study that evaluated long-term safety and effectiveness of lomitapide in HFHC, all were adults initiating therapy with lomitapide or who had done so within the previous 15 months. The registry is tracking lipid and safety data, including elevations of hepatic transaminases, symptomatic liver injury, and other hepatic markers. LOWER is a noninterventional study with all treatment decisions made at the discretion of the patients' health care providers. There are no protocol-mandated procedures or diagnostic tests.

The mean baseline low-density lipoprotein-cholesterol among the 163 patients who were being followed (mean age, 52 years; 56.4% female) was 234 mg/dL ± 96. Eighty-two percent were on

lipid-lowering drugs, and 11.7% were on apheresis. Lomitapide exposure duration was up to 47.1 months, with 72.4% receiving lomitapide for longer than 12 months and 38% for receiving it for two to five years. The mean dose was 10 mg daily (range, 5–40 mg). Dr. Larrey reported 25 hepatic events of special interest in 162 patients, with discontinuation of lomitapide for transaminase elevation in seven (4.3%). Hepatic transaminase elevations greater than three times the upper limit of normal (ULN) for longer than four weeks were reported in 17 patients (10.5%), and at five times or greater the ULN in 17 (10.5%). Elevated transaminases of three times the ULN (n = 35; 22.3%) resolved spontaneously or after dose reduction or drug discontinuation; however, no symptomatic liver injury was observed. Hepatic abnormalities were identified through imaging, biomarkers, liver biopsy, or other hepatic evaluation in six patients (3.7%).

While lomitapide was associated with asymptomatic transaminase increases, the percentages of increased levels of aspartate transaminase and alanine transaminase to greater than three times the ULN tended to be even lower than in the clinical study despite a doubled observation period, Dr. Larrey observed. He concluded, "There was no significant liver injury and no Hy's law cases, including in patients receiving a combination with other lipid-lowering agents."

Dr. Larrey also said that reductions in lomitapide dose or temporary interruptions in administration were associated with resolution, thereby allowing the continuation of treatment. Among study limitations, Dr. Larrey cited a lack of imaging data and ongoing assessment of fibrosis and histology, which would have given a fuller assessment of liver safety with lomitapide treatment.

## Impact of SIRT Plus Sorafenib on Overall Survival In Patients With Advanced Hepatocellular Carcinoma: The SORAMIC Trial Palliative Cohort

- Jens Ricke, MD, Maximilians University Munich, Munich, Germany

Although the addition of selective internal radiation therapy (SIRT) in the Sorafenib and Microtherapy Guided by Primovist-Enhanced MRI in Patients With Inoperable Liver Cancer (SORAMIC) trial did not result in significantly improved overall survival among patients with advanced hepatocellular carcinoma (HCC), some benefit was suggested in subgroup analyses, Dr. Ricke said in an International Liver Congress press briefing.

Although HCC, the most common form of primary liver cancer and the second most common cause of cancer-related death, can be treated with resection or transplantation, prognosis for the many patients who are not candidates for surgical interventions remains poor.

Patients were assigned to local ablation or a palliative cohort based on SORAMIC diagnostic components. In the palliative cohort, the objective was to determine the efficacy and safety of SIRT combined with sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals). Patients (N = 424) in this advanced HCC group had inoperable disease and were not candidates for transarterial chemoembolization. They were randomized to SIRT with yttrium-90 microspheres (SIR-Spheres, Sirtex Medical, Inc.) plus sorafenib (target dose, 400 mg twice daily) (n = 216) or sorafenib alone (n = 208). Overall survival was the primary endpoint.

An intention-to-treat analysis showed that in the SIRT-plus-sorafenib arm, median overall survival was 12.1 months; it was 11.5 months in the sorafenib-alone arm ($P$ = 0.93). In the per-protocol group, overall survival was 14.1 months and 11.1 months in the SIRT-plus-sorafenib (n = 114) and sorafenib-alone (n = 174) arms, respectively ($P$ = 0.25). Survival benefits were shown, however, in further analysis of the per-protocol population, specifically in patients younger than 65 years of age (hazard ratio [HR], 0.652), in those with a nonalcoholic cirrhosis etiology (HR, 0.632), and in those with no cirrhosis (HR, 0.465).

Adverse events of grade 3 or higher were reported in 115 of 159 (72.3%) patients in the SIRT-plus-sorafenib arm and in 135 of 197 (68.5%) patients in the sorafenib-alone arm.

While Dr. Ricke expressed disappointment that SIRT-plus-sorafenib did not meet the primary endpoint, he commented, "We believe our results have generated some very interesting new hypotheses in terms of the types of hepatocellular carcinoma patients that might benefit from combination therapy of SIRT and sorafenib, and we hope to explore these further in the future." ■